IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Mel Epstein and Kjesten A. Wiig	
Application No.:	10/003,740	Group Art Unit: 1614
Filed:	October 31, 2001	Examiner: Kwon, B.Y.S.
Confirmation No.:	2709	
For:	METHODS AND COMPOSITIONS FOR REGULATING MEMORY CONSOLIDATION AND METHODS OF USE THEREOF	

CERTIFICATE OF MAILING OR TRANSMISSION

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12/11/03 Carol M. Bowerman
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Carol M. Bowerman
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DECLARATION OF RANDALL L. CARPENTER, M. D., UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Randall L. Carpenter, M.D., of 39 Pine Ridge Road, Waban, Massachusetts, 02468, declare as follows:

A. I received my Doctor of Medicine degree from the University of Michigan Medical School, Ann Arbor, Michigan, in 1978. I received my Board Certification in Anesthesiology in 1986 and received an additional certification in Pain Management in 1994. My *curriculum vitae* is provided in Appendix I, attached.

B. Currently, I am the Chief Executive Officer of Sention, Inc. ("Sention"), in Providence, Rhode Island, where I have been employed since September, 2001. Sention is the assignee of the entire right, title and interest in U.S. Patent Application No. 10/003,740.

C. My responsibilities at Sention include, direction of scientific programs, including pre-clinical studies and human clinical trials, specifically with regard to initiating and designing investigations into methods to treat central nervous system conditions in humans, in particular, human clinical studies to improve memory following the administration of l-amphetamine.

D. I have read U.S. Patent Application No. 10/003,740 and the Office Action mailed from the U.S. Patent and Trademark Office, on August 13, 2003. I understand the application, the pending Office Action and the issues related to patentability presented by the Examiner in the Office Action for the invention claimed in the patent application.

E. I have read and I understand Gelowitz, *et. al., Pharmacology Biochemistry and Behavior 47:* 41-45 (1994) (hereinafter "Gelowitz"), Soetens, *et al., Neuroscience Letters, 161:* 9-12 (1993) (hereinafter "Soetens") and Brown, *et al., Behavioural Brain Research 114*: 135-143 (2000) (hereinafter "Brown"), all of which were cited by the Examiner in the Office Action dated August 13, 2003.

F. In support of the Reply to the Office Action, I hereby state the following:

1. Gelowitz, Soetens and Brown, do not describe a method of improving memory consolidation in a human by administering l-amphetamine, which is the subject matter of U.S. Patent Application No. 10/003,740.

2. Nothing in the methods, described by Gelowitz, Soetens and Brown, either alone or in combination, teach or suggest a method of improving memory consolidation in a human by administering l-amphetamine.

3. The modified Morris Water Maze Task, as employed by Gelowitz, does not specifically assess memory consolidation, particularly, memory consolidation in a human. The Water Maze Task, as employed by Gelowitz, may be assessing drug-induced improvements in motor function and vigor of the rats, which would not lead one of ordinary skill in the art to conclude that the improved performance observed by Gelowitz was a consequence of an improvement in memory consolidation. Based on the teachings of Gelowitz, one of ordinary skill in the art would not conclude that l-amphetamine would be useful to improve memory consolidation in a human.

4. Nothing in the methods described by Gelowitz, Soetens and Brown, either alone or in combination, would motivate one of ordinary skill in the art to employ l-amphetamine to improve memory consolidation in a human.

5. Further, nothing in the methods described by Gelowitz, Soetens and Brown, either alone or in combination, would lead one of ordinary skill in the art to reasonably expect success in improving memory consolidation in a human by treating the human with l-amphetamine.

6. Impairments in memory consolidation in humans are a common health problem; however, to date, other than the methods of Applicants' claimed invention, methods to improve memory consolidation in humans are inadequate and frequently associated with severe side effects such as addiction and adverse cardiovascular events. There has been an ongoing failure of others and a long-felt need to develop a method to improve memory consolidation in a human which has minimal side effects. U.S.

Patent Application No. 10/003,740 fills this long-felt need where others have failed.

7. As described in U.S. Patent Application No. 10/003,740, for example, on pages 90-97, and as shown in Figures 1, 8 and 13-15, the administration of l-amphetamine resulted in an unexpected effect compared to the effect of d-amphetamine. As shown in Figures 1 and 8, a 0.5 mg/kg dose of l-amphetamine (Figure 8) resulted in an unexpected effect on memory consolidation when compared to the effect observed with a 2.0 mg/kg dose of d-amphetamine (Figure 1). On page 43, Gelowitz describes l-amphetamine as a compound that is "considerably less active" than d-amphetamine. Thus, one of ordinary skill in the art would not reasonably expect that l-amphetamine, for example, at a dose one-fourth (¼) the dose of d-amphetamine, would improve memory consolidation similar to or better than an effect observed with d-amphetamine, as shown in U.S. Patent Application No. 10/003,740.

8. Sention has conducted additional experiments, since the filing of U.S. Application No. 10/003,740, which also show that l-amphetamine is generally equally efficacious in improving memory consolidation compared to d-amphetamine. Further, the doses of l-amphetamine required to achieve an efficacy observed with d-amphetamine are about one-half (½) to about one-fourth (¼), as shown in the instant application, the dose of d-amphetamine. One of ordinary skill in the art, based on the teachings of the art, including the teachings of Gelowitz, Soetens and Brown, would not have expected these results.

9. Sention has conducted Phase I clinical trials where humans were treated with l-amphetamine; and improvements in memory consolidation before and after treatment with l-amphetamine were assessed, as described in U.S. Patent Application No. 10/003,740. Using the techniques and doses

described in U.S. Patent Application No. 10/003,740, in Phase I clinical trials, the administration of l-amphetamine improved memory scores, indicative of an improvement in memory consolidation, compared to treatment with placebo, as shown in the Figures attached to this Declaration as Appendixes II and III. A brief description of the experimental procedure follows:

a. Two Phase I randomized, double-blind, placebo-controlled clinical studies to assess the effects of l-amphetamine on memory consolidation were conducted in normal healthy adult male (n=4) and female (n=12) subjects, with an age range of 21-72 years. The l-amphetamine was administered orally to the subjects and was about 99 mole percent l-amphetamine relative to the total content of amphetamine. The clinical studies also assessed the side effects of l-amphetamine.

b. There were five treatment periods in the clinical trials. Each treatment period was one week in duration and consisted of two consecutive days of treatment ("treatment period") with l-amphetamine (5 mg, 15 mg, 30 mg, 45 mg) or placebo, followed by five consecutive days without l-amphetamine or placebo ("washout period"). This treatment design is an ascending dose safety design with a placebo dose randomly inserted into the sequence. Each subject served as his or her own placebo control. Each subject was administered a single dose of one of the l-amphetamine doses (5 mg, 15 mg, 30 mg, 45 mg) or randomly assigned a placebo dose during each treatment period. Each subsequent treatment period included whatever dose of l-amphetamine (or placebo) had not previously been administered, until the subject had received each of the four l-amphetamine doses (5 mg, 15 mg, 30 mg, 45 mg) or a single placebo treatment to conclude the five week treatment period.

Indices of adverse effects (i.e., heart rate, blood pressure, tolerance, euphoria and addiction) were assessed after each dose in the treatment period.

c. Word recall, as determined by the Rey Auditory Visual Learning Test (RAVLT) (Rey, A., Arch Psychol 28:286-340 (1941); Lezak, M.D., Neuropsychological Assessment (3rd ed.), Oxford University Press, New York, NY (1995)) was employed to assess memory consolidation. RAVLT is an art recognized method to assess memory consolidation in humans. Word recall was assessed at two time points (30 minutes and 24 hours after exposure to an unrelated word list) during each treatment period. Word recall was not assessed during the washout period. The 30 minute memory score was made on the first day of treatment in each treatment period. Fifteen unrelated nouns were read to the subject by a third party followed by an interference or distraction trial, which was followed by a free-recall test of the fifteen unrelated nouns. After a 30-minute delay period, the subject was requested to recall the fifteen nouns (30 minute memory score). Twenty four (24) hours (± 2 hours) later, the subject was asked to recall the previously presented fifteen nouns (24 hour memory score).

d. As shown in Appendixes II and III, all subjects treated with l-amphetamine have memory scores greater than scores determined when they were treated with placebo 30 minutes and 24 hours after exposure to the unrelated word list.

e. As shown in Appendix II, humans treated with 30 mg and 45 mg of l-amphetamine had significantly improved memory 30-minute and 24-hour after exposure to the fifteen unrelated words ($p<0.05$) as determined by the Wilcoxon signed rank test.

f. As shown in Appendix III, a comparison of each subject's placebo score to his or her best score at any dose of l-amphetamine showed that memory performance (RAVLT score) for all subjects, except one, improved following treatment with l-amphetamine.

g. In addition, l-amphetamine was well tolerated in the subjects. Adverse side effects were minor and included dizziness, headache, insomnia, sinus tachycardia, supraventricular tachycardia and aptyalism. Side effects were generally mild and resolved without requiring medication, clinical intervention or hospitalization. No subject was removed from the study due to an adverse side effect.

10. Sention has conducted one Phase II clinical trial using a randomized, double-blind, placebo-controlled design where humans were treated with placebo or l-amphetamine (5 mg or 15 mg); and improvements in memory consolidation before and after treatment with l-amphetamine assessed employing the RAVLT method. A brief description of the experimental procedure employed in the Phase II clinical trial follows:

a. A Phase II randomized, double-blind, placebo-controlled clinical study was conducted in adult, memory impaired subjects (n=162) with an age range of 50-84 years. L-amphetamine (5 mg or 15 mg) or placebo was administered orally to different subjects once daily in the morning for twenty-eight (28) consecutive days. The clinical study also assessed the side effects of l-amphetamine.

b. Subjects were randomly assigned to one of three (3) treatment groups of about 50 subjects per group who received either placebo (Group I), 5 mg of l-amphetamine (Group II) or 15 mg of l-amphetamine (Group III) once daily for the twenty-eight consecutive days. Individual subjects did not serve as his or her

own placebo control or escalating l-amphetamine dose comparison. Indices of adverse affects (i.e., heart rate, blood pressure, tolerance, addiction) were assessed during the twenty-eight day treatment period and for fourteen days (± 4 days) after the twenty-eight day treatment period.

c. Word recall, as determined by RAVLT, as described above for Phase I clinical studies, was employed to assess memory consolidation thirty minutes and twenty-four hours following the administration of l-amphetamine or placebo. L-amphetamine at a dose of 5 mg or 15 mg daily for twenty-eight days did not result in an improvement in memory consolidation in this aged population of subjects.

d. As shown in Appendix II, 5 mg or 15 mg of l-amphetamine in Phase I clinical trials resulted in an improvement in memory consolidation which was significantly less than that observed at higher doses of l-amphetamine (30 mg, 45mg). Failure to observe an improvement in memory consolidation employing 5 mg or 15 mg doses of l-amphetamine in this aged human population may be a consequence of the Phase II study design. Unlike the Phase I clinical trials, in which each subject served as their own placebo control and escalating dose comparison, the Phase II study did not utilize each subject as their own placebo control or escalating l-amphetamine dose comparison. As a consequence, considerable between subject variability in RAVLT scores was observed, possibly masking a detectable effect of l-amphetamine on improving impairments in memory consolidation in this aged population in this study design.

e. Additional Phase II clinical trials will be conducted with higher doses of l-amphetamine (> 15 mg) and in humans of varying age

groups. The failure to observe a beneficial effect on improvements in memory consolidation following the administration of 5 mg or 15 mg of l-amphetamine in a single Phase II clinical trial is not unlike several Phase II clinical trials conducted to assess the efficacy of other clinically successful drugs, including ARICEPT®.

f. L-amphetamine administered to subjects in the Phase II clinical trials was generally well tolerated. The most common reported adverse effects included headache, dry mouth, insomnia, fatigue, nausea and flushing, all at relatively low percentages (about 4-9%) of the total population of subjects in the study.

11. None of the cited references, taken either separately or in combination, disclose or suggest Applicants' claimed method of improving memory consolidation in a human. Further, based on the teachings of Gelowitz, Soetens and Brown, taken either separately or in combination, one of ordinary skill in the art would not have expected the unexpected effects of Applicants' claimed method. In addition, based on the teaching of Gelowitz, Soetens and Brown, taken either separately or in combination, one of ordinary skill in the art would not reasonably expect to improve memory consolidation in a human by treatment with l-amphetamine. Thus, a method of improving memory consolidation in a human by treating the human with l-amphetamine, as claimed in the instant application, would not be obvious to one of ordinary skill in the art in light of the teachings of Gelowitz, Soetens and Brown, taken either separately or in any combination.

12. Further, the unexpected results of human Phase I clinical trials conducted by Sention show that memory consolidation can be improved in humans by treatment with l-amphetamine, thereby providing a method to improve memory consolidation in a human with minimal side effects, as claimed in

U.S. Application No. 10/003,740, which fills a long-felt need where others have failed.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements, if made, may jeopardize the validity of the application or any patent issuing thereon.

Randall L. Carpenter, M.D.

Dec 10, 2003

Date